PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SJB/PB60264	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2004/006604	International filing date *(day/month/year)* 17.06.2004	Priority date *(day/month/year)* 19.06.2003
International Patent Classification (IPC) or both national classification and IPC C07D207/26, C07D403/10, C07D417/12, C07D417/14, A61K31/402, A61K31/4025, A61P7/02		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.11.2004	24.10.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Traegler-Goeldel, M Telephone No. +49 89 2399-8278

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP2004/006604

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-88 as originally filed

Claims, Numbers

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 11 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-10,12
	No:	Claims	

2. Citations and explanations

see separate sheet

re item III:

Claim 11 is directed to methods for the treatment of the human or animal body. Under the terms of Rule 67.1 (iv) and Article 34 (4)a)i) PCT the International Preliminary Examination Authority is not required to carry out an examinations on such claims with respect to industrial applicability.

re item V:

1. Prior art

The examining procedure is based on the documents as cited by the Applicant and as cited in the International Search Report:

D2: WO 98/24784 A (CHOI SLEDESKI YONG MI ; PAULS HEINZ W (US); EWING WILLIAM R (US); SPAD) 11 June 1998 (1998-06-11)
D3: WO 03/043981 A (KLEANTHOUS SAVVAS ; YOUNG ROBERT JOHN (GB); SENGER STEFAN (GB); CHAN C) 30 May 2003 (2003-05-30)
D4: US-A-5 958 918 (CHOI-SLEDESKI YONG MI ET AL) 28 September 1999 (1999-09-28).

It is brought to the Applicant's attention that document D1, which entered the regional phase may be relevant for the consideration of novelty and for the consideration of inventive step for any subject matter entitled to the filing date only.

2. Novelty

The claimed 3-sulfonylaminopyrrolidine-2-one derivatives differ from those disclosed in documents D3 and D4 by the residue -X-Y in position 1, i.e. by an aminoalkyl substituted (hetero)arylresidue instead of an alkylamide (D3) and aminoalkylarylresidue bound via an alkylene bridge to the 1 position (D4). The present 1-aryl-3-sulfonyl-aminopyrrolidine-2-one derivatives differ form the ones as disclosed in document D2 indeed merely by the fact that residue R^x in the substituent Y which is $-C(R^x)(R^z)C_{0-2}alkylNR^cR^d$ represents alkyl optionally substituted with halogen whereas in D2 the corresponding residue X_5 or X_{5a} is a hydrogen atom or together form $=NR_5$. Therefore, the subject matter of claims 1 to 12 is considered

to fulfil the requirements of Art. 33 (2) PCT with respect to the cited prior art.

3. Inventive step

Documents D2 to D4 disclose 3-sulfonylamino-pyrrolidine-2-one derivatives that are potent inhibitors of factor Xa useful in the treatment of coagulation disorders as are the 3-sulfonylamino-pyrrolidine-2-one derivatives of the present application. The closest prior art is to be seen in document D2, since present claim 1 differs structurally merely by the replacement of a hydrogen atom by an C_{1-4}alkyl group as compared to the structurally closest compounds as generally disclosed in D2 (see item 2, above): the present compounds wherein R^1 is naphthalene, benzothienyl, phenyl and bithienyl differ only by this minor modification.

Thus, if the problem underlying the present application were to be seen in provision of further compounds that may be used as inhibitors of factor Xa, the solution of the problem must be considered as being obvious, since the claimed subject matter represents merely a minor modification from the compounds according to D2 used for exactly the same purpose or may as well be seen as a combination of the main basic 1-aryl-3-sulfonyl-pyrrolidine-2-one structure known from D2 with the sulfonyl-aminoresidues **R^6 from D3 all being identical to the corresponding residues R^1 in present claim 1**, some of which are additionally disclosed as being preferred in D4 (e.g. see claim 48).

The argumentation of the Applicant, as set out in the letter of 26.11.04 is not convincing for the following reasons: The Applicant has argued that there were no motivation for the skilled person to select the a 1-aryl-3-sulfonyl-pyrrolidine-2-one structure wherein n = 0 to combine with the sulfonylamino residues as disclosed in D3 or D4. But in document D2 it is clearly disclosed that the compounds disclosed therein wherein n is zero do have the alleged activity and are comprised main claim 1; the fact that n is 1 in all exemplified compounds does not mean that the skilled person would have considered the compounds wherein n is zero to be inactive. Although there is no specific process given for the compounds wherein n is zero, the process for those wherein n is 1 may easily be adapted to the ones wherein n is zero, since this position of the molecule is not involved in the process leading to the desired compound.

The fact that D2 and D4 state a preference for the compounds wherein X_5 and X_{5a} together form $=NR_5$ does not mean that the compounds wherein X_5 and X_{5a} are both

hydrogen are not active, since first of all comprised by main claim 1 and especially in view of the fact that there are several exemplified compounds disclosed in D2 bearing this feature;

Thus, if the skilled man were to change the compounds known from D2 as little as possible from the structural point of view (in order to retain the pharmacological activity) without coming to compounds already comprised by document D2 , the selection of n being zero in combination with the aminosulfonyl residues (R^6) as known from D3 (same activity) which are completely identical with the aminosulfonyl residues (R^1) in present claim 1 is an inevitable result of such considerations. Therefore, the compounds according to claim 1 represent merely minor modifications of the compounds known from D2 and/or a combination of documents D2 and D3 and consequently do not involve an inventive step. In view of the minor variation introduced to the present compounds in comparison to the pertinent prior art compounds of D2 and D3 the Examining Division is of the opinion that not only total predictability renders a technical proposal obvious, but also the reasonable expectation of the attained result, which is required by the stated problem, may well be conclusive against the recognition of an inventive step, in particular in the absence of prejudice or difficulties.

Therefore, re that very close prior art D2 (structurally and concerning properties), the problem underlying this part of the application, the solution of which could involve an inventive step, is to be seen in the provision of compounds that do exhibit an unexpected or improved effect (of better pharmacological characteristics) compared to the closest prior art D2. The Applicant's attention was drawn to the fact, that any comparative tests should be made with compounds of the closest prior art, showing the closest possible structural similarity. The Applicant has not provided any data showing such an effect. Therefore, the present application does not fulfil the requirements of Art. 33 (3) PCT.

4. Industrial applicability

No objection arises as far as the compounds according to claim 1 may be used for the production of pharmaceutical products.